

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification</b> <sup>6</sup> : <b>A61K 31/557 // (A61K 31/557, 31:557)</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/23225</b> <b>(43) International Publication Date:</b> 3 July 1997 (03.07.97)
<b>(21) International Application Number:</b> PCT/US96/18235 <b>(22) International Filing Date:</b> 15 November 1996 (15.11.96)  <b>(30) Priority Data:</b> 08/577,039 22 December 1995 (22.12.95) US  <b>(71) Applicant:</b> ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US).  <b>(72) Inventors:</b> DEAN, Thomas, R.; 101 Meadow View Court, Weatherford, TX 76087 (US). HELLBERG, Mark; 5211 Overridge Drive, Arlington, TX 76017 (US). SALLEE, Verney, L.; 304 Diamond Lane Road, Burleson, TX 76028 (US).  <b>(74) Agents:</b> MAYO, Michael, C. et al.; Alcon Laboratories, Inc., Patent Dept., Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).		<b>(81) Designated States:</b> AU, CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> COMBINATIONS OF DP AND FP TYPE PROSTAGLANDINS FOR LOWERING IOP  <b>(57) Abstract</b>  Compositions containing DP-agonist and FP-agonists prostaglandin agonists and methods of their use in treating glaucoma or ocular hypertension are disclosed.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

5

## Combinations of DP and FP Type Prostaglandins For Lowering IOP

10

The present invention relates to the treatment of glaucoma and ocular hypertension. In particular, the present invention relates to the use of combinations of prostaglandin D-series and prostaglandin F-series compounds to treat glaucoma and hypertension.

### Background of the Invention

15

Glaucoma is a progressive disease which leads to optic nerve damage, and, ultimately, total loss of vision. The causes of this disease have been the subject of extensive studies for many years, but are still not fully understood. The principal symptom of and/or risk factor for the disease is elevated intraocular pressure or ocular hypertension due to excess aqueous humor in the anterior chamber of the eye.

20

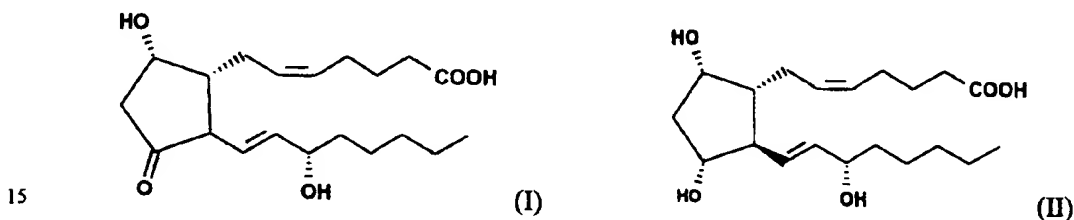
The reasons why aqueous humor accumulates are not fully understood. It is known that the elevated intraocular pressure ("IOP") can be at least partially controlled by administering drugs which reduce either the production of aqueous humor within the eye, such as beta-blockers and carbonic anhydrase inhibitors, or increase the flow of aqueous humor out of the eye, such as miotics and sympathomimetics.

25

All types of drugs currently being used to treat glaucoma have potentially serious side effects. Miotics such as pilocarpine can cause blurring of vision and other visual side effects, which may lead either to decreased patient compliance or to termination of therapy. Systemically administered carbonic anhydrase inhibitors can also cause serious side effects,

such as nausea, dyspepsia, fatigue, and metabolic acidosis which can affect patient compliance and/or necessitate the withdrawal of treatment. Moreover, some beta-blockers have increasingly become associated with serious pulmonary side effects attributable to their effects on beta-2 receptors in pulmonary tissue. Sympathomimetics cause tachycardia, arrhythmia and hypertension. There is therefore a continuing need for therapies which control the elevated intraocular pressure associated with glaucoma.

Prostaglandins, which are metabolite derivatives of arachidonic acid, have recently been pursued for possible efficacy in lowering IOP. The arachidonic acid cascade is initiated by the conversion of arachidonic acid to prostaglandin  $G_2$  and subsequent conversion to prostaglandin  $H_2$ . Other naturally occurring prostaglandins are derivatives of prostaglandin  $H_2$ . A number of different types of prostaglandins have been discovered including A, B, D, E, F and I-Series prostaglandins. Of interest in the present invention are combinations of compounds which exhibit similar IOP lowering mechanisms as  $PGD_2$ , formula (I) and  $PGF_{2\alpha}$ , formula (II):



The relationship between  $PGD_2$  receptor activation and IOP lowering effects is not well known. Various publications have reported that  $PGD_2$  receptor activation leads to second messenger activation and in particular, to the stimulation of adenylate cyclase and resultant increases in cAMP levels (Thierauch, *Prostaglandins and their Receptors: II. Receptor Structure and Signal Transduction*, Journal of Hypertension, volume 12, pages 1-5 (1994). Regardless of mechanism,  $PGD_2$  has been shown to lower IOP (Nakajima,

*Effects of Prostaglandin D<sub>2</sub> and its analogue, BW245C, on Intraocular Pressure in Humans*, Graefe's Archive Ophthalmology, volume 229, pages 411-413 (1991)). Thus, it has been of interest in the field to develop synthetic PGD<sub>2</sub> analogues with IOP lowering efficacy.

5        Synthetic PGD<sub>2</sub>-type analogs have been pursued in the art (Graefe's Archive Ophthalmology, volume 229, pages 411-413 (1991)). Though PGD<sub>2</sub>-type molecules lower IOP, these types of molecules have also been associated with undesirable side effects resulting from topical ophthalmic dosing. Such effects have included an initial increase in IOP, conjunctival hyperemia, increases in microvascular permeability, and increases in  
10        eosinophile infiltration (Alm, *The Potential of Prostaglandin Derivatives in Glaucoma Therapy*, Current Opinion in Ophthalmology, volume 4, No. 11, pages 44-50 (1993)). The binding of other types of molecules with the PGD<sub>2</sub> receptor may lead to IOP lowering effects, but with fewer or reduced side effects than the above mentioned PGD<sub>2</sub>-type analogs.

15        The relationship of PGF<sub>2α</sub> receptor activation and IOP lowering effects is not well known. It is believed that PGF<sub>2α</sub> receptor activation leads to increased outflow of aqueous humor. Regardless of mechanism, PGF<sub>2α</sub> and analogs have been shown to lower IOP (Giuffre, *The Effects of Prostaglandin F<sub>2α</sub> the Human Eye*, Graefe's Archive Ophthalmology, volume 222, pages 139-141 (1985); and Kerstetter et al., *Prostaglandin  
20        F<sub>2α</sub>-1-Isopropylester Lowers Intraocular Pressure Without Decreasing Aqueous Humor Flow*, American Journal of Ophthalmology, volume 105, pages 30-34 (1988)). Thus, it has been of interest in the field to develop synthetic PGF<sub>2α</sub> analogs with IOP lowering efficacy.

Synthetic PGF<sub>2α</sub> -type analogs have been pursued in the art (Graefe's Archive Ophthalmology, volume 229, pages 411-413 (1991)). Though PGF<sub>2α</sub>-type molecules lower IOP, these types of molecules have also been associated with undesirable side effects resulting from topical ophthalmic dosing. Such effects include an initial increase in IOP, breakdown of the blood aqueous barrier and conjunctival hyperemia (Alm, *The Potential of Prostaglandin Derivatives in Glaucoma Therapy*, Current Opinion in Ophthalmology, volume 4, No. 11, pages 44-50 (1993)). The binding of other types of molecules with the PGF<sub>2α</sub> receptor may lead to IOP lowering effects, but with less side effects than those elicited by the above mentioned PGF<sub>2α</sub>-type analogs.

Based on the foregoing, a need exists for the development of molecules that will activate the PGD<sub>2</sub> and PGF<sub>2α</sub> receptors, yielding a more efficacious lowering of IOP, while exhibiting fewer or reduced side effects.

#### Summary of the Invention

The present invention is directed to compositions and methods of their use in treating IOP and ocular hypertension. In particular, the present invention provides combinations of DP-agonists (hereinafter defined) and FP-agonists (hereinafter defined), and methods of their use in treating glaucoma and ocular hypertension.

The present invention takes advantage of the use of two different prostaglandin-type molecules for lowering IOP. In administering these compounds in a combination composition, the amounts of each compound can be decreased, thus reducing side effects

attributable to higher quantities of the individually dosed compounds, while achieving the same or greater effect on lowering IOP.

#### Detailed Description of the Invention

5

The present invention makes use of a combination of a DP-agonist and a FP-agonist for lowering IOP. While Applicants do not wish to be bound by any theory, the D-prostaglandins ("DP-agonist") are believed to inhibit aqueous humor inflow into the eye, while the F-prostaglandins ("FP-agonist") are believed to increase the outflow of aqueous  
10 humor from the eye. Therefore, the use of a combination of a DP-agonist and a FP-agonist may lead to more efficacious lowering of IOP, and a reduced magnitude of side effects.

The DP-agonists of the present invention are useful in lowering IOP in humans and other mammals. The DP-agonists of the present invention are functionally defined by their ability to bind to prostaglandin-D<sub>2</sub> receptors of cells and evoke similar responses as when  
15 PGD<sub>2</sub> binds these receptors, inducing the lowering of IOP. Various assays may be used for the determination of DP-agonists.

Binding assays may be used to elucidate DP-agonists of the present invention. Sharif has described a receptor binding assay in: Sharif, N.A., Williams, G.W. and DeSantis, L.M, Neurochemistry Research, volume 20, pages 669-674 (1995), the entire  
20 contents of which are incorporated herein by reference, and may be modified as described below, for the elucidation of DP-agonists of the present invention. Briefly, the binding assays are conducted in 25 mM Tris HCl (pH 7.4) containing 138 mM NaCl, 5 mM MgCl<sub>2</sub>, and 1 mM EDTA. Frozen-thawed expired human blood platelets (40-60 mg/ml stock) are

incubated in a total volume of 500  $\mu$ l with 2-10 nM [ $^3$ H]PGD<sub>2</sub> in the absence and presence of 100  $\mu$ M unlabeled PGD<sub>2</sub> to define total and non-specific binding, respectively. The incubations (20 minutes at 23°C) are terminated by rapid vacuum filtration, using a Whatman GF/B glass fiber filter previously soaked in 1% polyethyleneimine and 0.1% BSA, and the receptor-bound radioactivity is then determined by scintillation spectrometry. The binding data are analyzed using a non-linear, iterative curve-fitting computer program to define the receptor binding affinity ( $K_i$ ) of the compounds. Compounds which exhibit  $K_i$  values in this assay of less than or equal to about 20  $\mu$ M are within the definition of DP-agonists of the present invention.

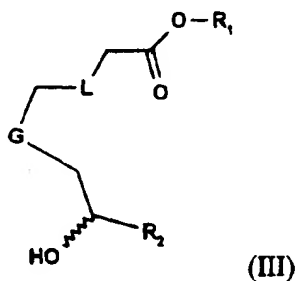
10       The DP-agonists of the present invention may also be defined functionally, by their ability to stimulate adenylate cyclase activity. Sharif has described this type of functional assay in: Sharif, N.A., Xu, S. and Yanni, J.M., Journal of Ocular Pharmacology, volume 10, pages 653-664 (1994), the entire contents of which are incorporated herein by reference, and which may be modified as described below, for the elucidation of DP-agonists of the present invention. Briefly, functional adenylate cyclase activity is determined using embryonic bovine tracheal cells (EbTr) cells. Cultured cells are stimulated with the test compound for 15 minutes at 23°C. The reaction is then stopped and the cAMP generated is determined by a radioimmunoassay kit. Data are analyzed using a non-linear, iterative curve-fitting computer program to define the potency ("EC<sub>50</sub>", 15 concentration which produces 50% of the maximum response of PGD<sub>2</sub>) and efficacy of the compounds. Compounds which exhibit EC<sub>50</sub> values of less than or equal to about 10  $\mu$ M are within the DP-agonist definition of the present invention.

20



It has unexpectedly been found that 3-Oxa-D-prostaglandins ("3-O-DP") are more efficacious in lowering and controlling IOP than their 3-carba analogs. Consequently, these 3-O-DPs can be administered at lower doses than their 3-carba analogs. The lower doses are believed to reduce their activity on other prostaglandin receptors and thereby reduce many of the aforementioned undesirable side effects.

Preferred DP-agonists of the present invention are of the following formula (III):



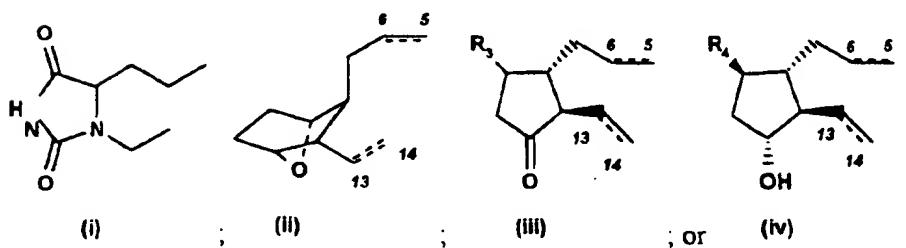
wherein:

$R_1$  is H, alkyl or alkylcycloalkyl;

$R_2$  is alkyl, cycloalkyl or alkylcycloalkyl;

L is carbon or oxygen; and

G is

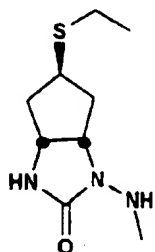


wherein:

$R_3$  is H, OH or alkyl;

$R_4$  is H, F, Cl, I, or  $C_{1-3}$  alkyl;

---- represents a single bond or double bond; provided that when a double bond is between the 13 and 14 position it is in the *trans* configuration; when L is carbon, G may also be



(v) ; and

pharmaceutically acceptable salts thereof.

More preferably, the DP-agonists of the present invention are those of formula (III), wherein one or more of the following substituents is selected:

G is (ii) or (iv);

R<sub>4</sub> is Cl;

R<sub>2</sub> is cyclohexyl;

L is oxygen;

R<sub>1</sub> is isopropyl; and

the bond between the 5 and 6 position is a *cis* configured double bond.

The most preferred DP-agonist of the present invention is of formula (III) wherein: G is (iv); R<sub>4</sub> is Cl; R<sub>2</sub> is cyclohexyl; L is oxygen; R<sub>1</sub> is isopropyl; the bond between position 13 and 14 is saturated; and the bond between the 5 and 6 position is a *cis* configured double bond. Some of the DP-agonists of the present invention are believed to be novel.

The DP-agonists of the present invention, aside from those compounds which are believed to be novel, are known to those skilled in the art, and some are available commercially or may be made by methods known to those skilled in the art. Novel

compounds of the present invention may be prepared by analogous synthetic routes as those which are known.

The DP-agonists wherein G is formula (i), are described in in Barraclough, *Synthesis and Platelet Aggregation Inhibiting Activity of Acid Side-chain Modified Hydantoin Prostaglandin Analogues*, Archives in Pharmacology, volume 326, No. 2, 5 pages 85-95 (1993), the entire contents of which are incorporated herein by reference.

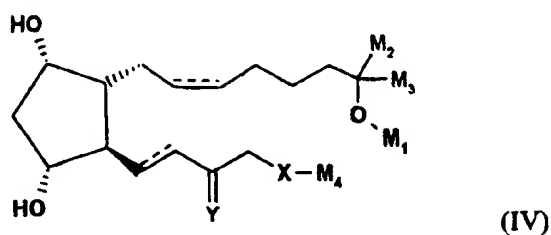
The DP-agonists wherein G is formula (ii), may be prepared from [1S-[1 $\alpha$ , 2 $\alpha$ (Z), 3 $\alpha$  (1E, 3S), 4 $\alpha$ ]]-7-[3-(3-Cyclohexyl-3-hydroxy-1-propenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid following the procedure described in Das, *9,11-Epoxy-9-homoprostanoic Acid Analogues as Thromboxane A<sub>2</sub> Receptor Antagonists*, Journal of Medicinal Chemistry, volume 33, No. 6, pages 1741-1748 (1990), for the conversion of [1S-[1 $\alpha$ , 2 $\alpha$ (Z), 3 $\alpha$  (1E, 3S, 4R)), 4 $\alpha$ ]]-7-[3-[4-phenyl-3-(tetrahydropyran-2-yloxy)-1-pentyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid to [1S-[1 $\alpha$ , 2 $\alpha$ (Z), 3 $\alpha$  (1E, 3S, 4R)), 4 $\alpha$ ]]- 10 [[4-[3-(3-hydroxy-4-phenyl-1-pentyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid.

15 The DP-agonists wherein G is formula (iii), may be prepared from (5Z, 13E)-9S, 11R, 15S)-15 cyclohexyl-9-hydroxy-3-oxa-11,15-bis (tetrahydropyran-2-yloxy)-16, 17, 18, 19, 20-pentanor -5,13-prostanoic acid tert butyl ester (EP 299 914) by the method described in Bundy, *Synthesis and Platelet Aggregation Inhibiting Activity of Prostaglandin D Analogues*, Journal of Medicinal Chemistry, volume 26, pages 790-799 20 (1983), the entire contents of which are incorporated herein by reference.

The DP-agonists wherein G is formula (iv) are disclosed in WIPO Publication NO. WO 94/05631, and is incorporated herein by reference to the extent this publication teaches the synthesis of the compounds contained therein.

The DPs of the present invention wherein G is (v) are disclosed in European Patent Application Publication No. 0 458 642 A1, and is incorporated herein by reference to the extent this publication teaches the synthesis of the compounds contained therein.

5 The FP-agonists of the present invention are useful in lowering IOP in humans and other mammals. The FP-agonists of the present invention are of the following formula (IV):



10

wherein:

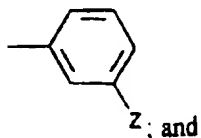
X is CH<sub>2</sub> or O;

Y is H and OH or O;

15 M<sub>1</sub> is H, C<sub>1-12</sub> straight-chain or branched alkyl; C<sub>1-12</sub> straight chain or branched acyl; C<sub>3-8</sub> cycloalkyl; a cationic salt moiety; or an acceptable amine moiety;

M<sub>2</sub> and M<sub>3</sub> are H or taken together are (=O); and

M<sub>4</sub> is C<sub>3-5</sub> alkyl or



20

Z is H, Cl or CF<sub>3</sub>;

provided that when  $M_2$  and  $M_3$  taken together are (=O), then  $M_1$  cannot be  $C_{1-12}$  straight chain or branched acyl; and when  $M_2$  and  $M_3$  are H, then  $M_1$  cannot be a salt or an amine.

5       The following are preferred FP-agonists of formula (IV): the esters latanoprost and UFO-21, as well as, cloprostenol, fluprostenol, 13,14 dihydro-cloprostenol and 13, 14-dihydrofluprostenol and their isopropyl esters and salts.

The most preferred FP-agonist of the present invention is latanoprost.

10       The FP-agonists of the present invention are known and are commercially available, or may be prepared by known methods to those skilled in the art. Some of the FP-agonists of the present invention are disclosed in European Patent Publication No. 0 639 563 A2, which is incorporated herein by reference to the extent that it discloses methods of synthesizing or obtaining FP-agonists of the present invention.

15       The combinations of a DP-agonist and a FP-agonist of the present invention are useful in lowering intraocular pressure and thus are useful in the treatment of glaucoma. As compared with therapeutically effective dosages of the individual components, the combinations produce significantly fewer unwanted side effects such as marked vasoconstriction or vasodilation of the vessels of the sclera, painful stinging and intraocular inflammation.

20       The DP-agonists and FP-agonists of the present invention may be formulated either separately or in the same pharmaceutical compositions. Thus, the DP-agonists and FP-agonists of the present invention can be administered simultaneously or sequentially to humans and other mammals as a treatment of glaucoma or ocular hypertension. When formulated separately the DP-agonists and FP-agonists of the present invention may be

administered 1) concomitantly; 2) within a short delay between one agent and the other; 3) in an offset manner, such as the DP-agonist in the morning and the FP-agonist in the evening, or in reverse order; and 4) such that the DP-agonist is dosed both in the morning and evening and FP-agonist is dosed in the evening. It is preferred that the DP-agonist be  
5 dosed first and shortly thereafter (i.e., 5-30 minutes) the FP-agonist be dosed.

The DP-agonists and FP-agonists of the present invention are useful in lowering intraocular pressure and thus are useful in the treatment of glaucoma. The preferred route of administration is topical. As used herein, the term "pharmaceutically effective amount" refers to that amount of a DP-agonist and FP-agonist formulated separately, or a  
10 combination of a DP-agonist and FP-agonist formulated together, which lowers IOP when administered to a mammal. The compounds of the present invention can be administered as solutions, suspensions, or emulsions (dispersions) in a suitable ophthalmic vehicle.

In forming compositions for topical administration, the compounds of the present invention are generally formulated as between about 0.00005 to about 0.5 percent by  
15 weight (wt%) solutions in water at a pH between 4.5 to 7.4. The compounds are preferably formulated between about 0.0003 to about 0.3 wt% and, most preferably, between about 0.0005 and about 0.03 wt%. While the precise regimen is left to the discretion of the clinician, it is recommended that the resulting solution or solutions be topically applied by placing one drop of each solution(s) in each eye one or two times a  
20 day.

Other ingredients which may be desirable to use in the ophthalmic preparations of the present invention include preservatives, co-solvents and viscosity building agents.

Preferred formulations of DP-agonists and FP-agonists combinations of the present invention include the following Examples 1-3:

**Example 1**

5	<b>Ingredient</b>	<b>Amount (wt%)</b>
	DP-agonist	0.001
	FP-agonist	0.001
	Phosphate Buffered Saline	1.0
10	Benzalkonium Chloride	0.01
	Polysorbate 80	0.5
	Purified water	q.s. to 100%

15

**Example 2**

An example of two formulations to be used concomitantly, within 30 minutes, or offset by more than 1 hour.

20

**Formulation A**

	<b>Ingredient</b>	<b>Amount (wt%)</b>
	DP-agonist	0.001
25	Monobasic sodium phosphate	0.05
	Dibasic sodium phosphate (anhydrous)	0.15
	Sodium chloride	0.75
	Disodium EDTA (Edetate disodium)	0.05
30	Cremophor EL	0.1
	Benzalkonium chloride	0.01
	HCl and/or NaOH	pH 7.3 - 7.4
	Purified water	q.s. to 100%

## Formulation B

5	<b>Ingredient</b>	<b>Amount (wt%)</b>
	FP-agonist	0.001
	Monobasic sodium phosphate	0.05
	Dibasic sodium phosphate (anhydrous)	0.15
10	Sodium chloride	0.75
	Disodium EDTA (Edetate disodium)	0.05
	Cremophor EL	0.1
	Benzalkonium chloride	0.01
	HCl and/or NaOH	pH 7.3 - 7.4
15	Purified water	q.s. to 100%

## Example 3

20	<b>Ingredient</b>	<b>Amount (wt%)</b>
	DP-agonist	0.0005
	FP-agonist	0.0005
25	Phosphate Buffered Saline	1.0
	Hydroxypropyl- $\beta$ -cyclodextrin	4.0
	Purified water	q.s. to 100%

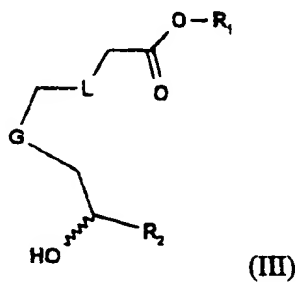


What is claimed is:

1. A method of treating glaucoma or ocular hypertension in mammals which comprises administering to the mammal:

5

(a) a pharmaceutically effective amount of one or more DP-agonists of formula (III):



10

wherein:

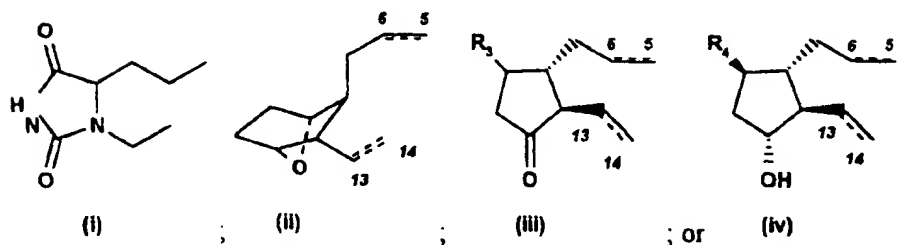
R<sub>1</sub> is H, alkyl or alkylcycloalkyl;

R<sub>2</sub> is alkyl, cycloalkyl or alkylcycloalkyl;

15

L is carbon or oxygen; and

G is



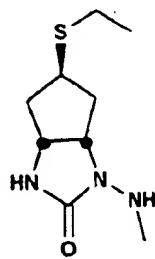
20

wherein:

R<sub>3</sub> is H, OH or alkyl;

R<sub>4</sub> is H, F, Cl, I, or C<sub>1-3</sub> alkyl;

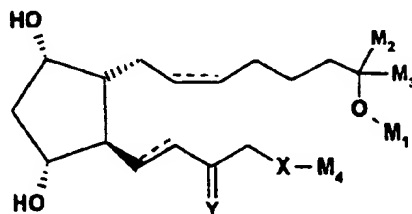
--- represents a single bond or double bond; provided that when a double bond is between the 13 and 14 position it is in the *trans* configuration;  
when L is carbon, G may also be



(v) ; and

pharmaceutically acceptable salts thereof; and

(b) a pharmaceutically effective amount of one or more FP-agonists of formula (IV):



(IV)

wherein:

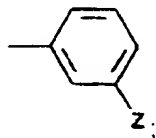
X is CH<sub>2</sub> or O;

Y is H and OH or O;

M<sub>1</sub> is H, C<sub>1-12</sub> straight-chain or branched alkyl; C<sub>1-12</sub> straight chain or branched acyl; C<sub>3-8</sub> cycloalkyl; a cationic salt moiety; or an acceptable amine moiety;

M<sub>2</sub> and M<sub>3</sub> are H or taken together are (=O); and

M<sub>4</sub> is C<sub>3-5</sub> alkyl or



Z is H, Cl or CF<sub>3</sub>; and

provided that when  $M_2$  and  $M_3$  taken together are  $(=O)$ , then  $M_1$  cannot be  $C_{1-12}$  straight chain or branched acyl; and when  $M_2$  and  $M_3$  are H, then  $M_1$  cannot be a salt or an amine.

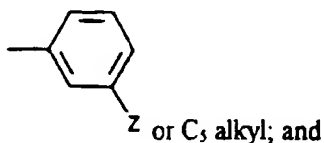
- 5            2.        The method of claim 1 wherein the DP agonist is selected from the group consisting of molecules containing one or more of the following substituents:

G is (iv);  $R_4$  is Cl;  $R_2$  is cyclohexyl; L is oxygen;  $R_1$  is isopropyl; the bond between position 13 and 14 is saturated; and the bond between the 5 and 6 position is a *cis* configured double bond.

10

3.        The method of claim 1 wherein the FP-agonist is selected from the group consisting of molecules containing one or more of the following substituents:

$M_1$  is H or isopropyl;  $M_2$  and  $M_3$  taken together are  $(=O)$ ;  $M_4$  is



- 15            Z is H, Cl or  $CF_3$ .

4.        The method of claim 2 wherein the DP-agonist has the formula wherein G is (iv);  $R_4$  is Cl;  $R_2$  is cyclohexyl; L is oxygen;  $R_1$  is isopropyl; the bond between position 13 and 14 is saturated; and the bond between the 5 and 6 position is a *cis* configured double bond.

20

5.        The method of claim 3 wherein the FP-agonist is selected from the group consisting of: latanoprost and UFO-21; and cloprostenol, fluprostenol, 13,14 dihydro-cloprostenol, 13, 14-dihydrofluprostenol and their isopropyl esters and salts thereof.

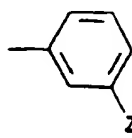
25

6. The method of claim 1 wherein,

(a) the DP-agonist is selected from the group consisting of molecules containing one or more of the following substituents: G is (iv); R<sub>4</sub> is Cl; R<sub>2</sub> is cyclohexyl; L is oxygen; R<sub>1</sub> is isopropyl; the bond between position 13 and 14 is saturated; and the bond between the 5 and 6 position is a *cis* configured double bond; and

(b) the FP-agonist is selected from the group consisting of molecules containing one or more of the following substituents:

M<sub>1</sub> is H or isopropyl; M<sub>2</sub> and M<sub>3</sub> taken together are (=O); M<sub>4</sub> is



Z or C<sub>3</sub> alkyl; and

Z is H, Cl or CF<sub>3</sub>.

7. The method of claim 6 wherein:

(a) the DP-agonist has the formula wherein G is (iv); R<sub>4</sub> is Cl; R<sub>2</sub> is cyclohexyl; L is oxygen; R<sub>1</sub> is isopropyl; the bond between position 13 and 14 is saturated; and the bond between the 5 and 6 position is a *cis* configured double bond; and

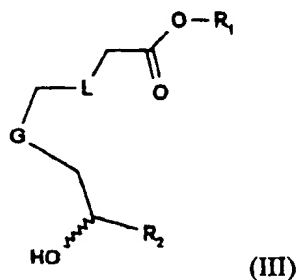
(b) the FP-agonist is selected from the group consisting of: latanoprost and UFO-21; and cloprostenol, fluprostenol, 13,14 dihydro-cloprostenol, 13, 14-dihydrofluprostenol and their isopropyl esters and salts thereof.

8. The method of claim 1 wherein the DP-agonist and FP-agonist are contained in one pharmaceutical composition.

9. The method of claim 1 further comprising administering the DP-agonist and FP-agonist concomitantly, within about 5 to 30 minutes from each other or greater than 2 hours from each other.

10. A composition for treating glaucoma or ocular hypertension in mammals comprising a pharmaceutically acceptable carrier containing:

(a) a pharmaceutically effective amount of one or more DP-agonists of formula (III):



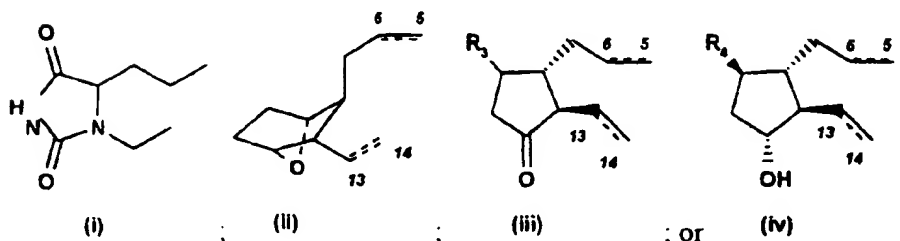
wherein:

$R_1$  is H, alkyl or alkylcycloalkyl;

$R_2$  is alkyl, cycloalkyl or alkylcycloalkyl;

L is carbon or oxygen; and

G is



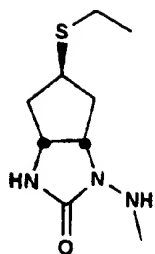
wherein:

$R_3$  is H, OH or alkyl;

$R_4$  is H, F, Cl, I, or  $C_{1-3}$  alkyl;

--- represents a single bond or double bond; provided that when a double bond is between the 13 and 14 position it is in the *trans* configuration;

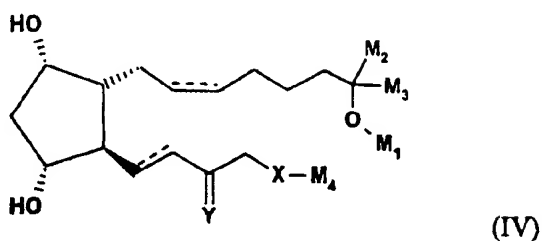
when L is carbon, G may also be



(v) ; and

pharmaceutically acceptable salts thereof; and

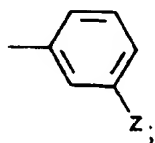
- 5 (b) a pharmaceutically effective amount of one or more FP-agonists of formula (IV):



(IV)

wherein:

- 10 X is CH<sub>2</sub> or O;  
 Y is H and OH or O;  
 M<sub>1</sub> is H, C<sub>1-12</sub> straight-chain or branched alkyl; C<sub>1-12</sub> straight chain or branched acyl; C<sub>3-8</sub> cycloalkyl; a cationic salt moiety; or an acceptable amine moiety;  
 M<sub>2</sub> and M<sub>3</sub> are H or taken together are (=O); and  
 15 M<sub>4</sub> is C<sub>3-5</sub> alkyl or



Z is H, Cl or CF<sub>3</sub>; and

provided that when  $M_2$  and  $M_3$  taken together are (=O), then  $M_1$  cannot be  $C_{1-12}$  straight chain or branched acyl; and when  $M_2$  and  $M_3$  are H, then  $M_1$  cannot be a salt or an amine.

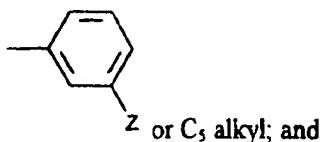
5 11. The composition of claim 10 wherein the DP agonist is selected from the group consisting of molecules containing one or more of the following substituents:

G is (iv);  $R_4$  is Cl;  $R_2$  is cyclohexyl; L is oxygen;  $R_1$  is isopropyl; the bond between position 13 and 14 is saturated; and the bond between the 5 and 6 position is a *cis* configured double bond.

10

12. The composition of claim 10 wherein the FP-agonist is selected from the group consisting of molecules containing one or more of the following substituents:

$M_1$  is H or isopropyl;  $M_2$  and  $M_3$  taken together are (=O);  $M_4$  is



15

Z is H Cl, or  $CF_3$ .

13. The composition of claim 11 wherein the DP-agonist has the formula wherein G is (iv);  $R_4$  is Cl;  $R_2$  is cyclohexyl; L is oxygen;  $R_1$  is isopropyl; the bond between position 13 and 14 is saturated; and the bond between the 5 and 6 position is a *cis* configured double bond.

20

14. The composition of claim 12 wherein the FP-agonist is selected from the group consisting of: latanoprost and UFO-21; and cloprostenol, fluprostenol, 13,14 dihydro-cloprostenol, 13, 14-dihydrofluprostenol and their isopropyl esters and salts thereof.

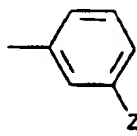
25

15. The composition of claim 10 wherein:

(a) the DP agonist is selected from the group consisting of molecules containing one or more of the following substituents: G is (iv); R<sub>4</sub> is Cl; R<sub>2</sub> is cyclohexyl; L is oxygen; R<sub>1</sub> is isopropyl; the bond between position 13 and 14 is saturated; and the bond between the 5 and 6 position is a *cis* configured double bond; and

(b) the FP-agonist is selected from the group consisting of molecules containing one or more of the following substituents:

M<sub>1</sub> is H or isopropyl; M<sub>2</sub> and M<sub>3</sub> taken together are (=O); M<sub>4</sub> is



Z or C<sub>3</sub> alkyl; and

10 Z is H, Cl or CF<sub>3</sub>.

16. The composition of claim 15 wherein:

(a) the DP-agonist has the formula wherein G is (iv); R<sub>4</sub> is Cl; R<sub>2</sub> is cyclohexyl; L is oxygen; R<sub>1</sub> is isopropyl; the bond between position 13 and 14 is saturated; and the bond between the 5 and 6 position is a *cis* configured double bond; and

(b) The FP-agonist is selected from the group consisting of: latanoprost and UFO-21; and cloprostenol, fluprostenol, 13,14 dihydro-cloprostenol, 13, 14-dihydrofluprostenol and their isopropyl esters and salts thereof.



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/18235

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/557 //(A61K31/557,31:557)

According to International Patent Classification (IPC) or to both national classification and IPC:

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 603 800 A (ALCON LAB INC) 29 June 1994 * see in particular page 2, lines 34-55 *	1 -16
Y	EP 0 308 135 A (UENO SEIYAKU OYO KENKYUJO KK) 22 March 1989 * see in particular the claims and page 10, lines 34-42 *	1 -16
A	CURRENT OPINION IN OPHTHALMOLOGY, vol. 4, no. 11, 1993, pages 44-50, XP000651955 ALM A.: "The potential of prostaglandin derivates in glaucoma therapy" cited in the application * see in particular page 48, right col. *	1-16
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*B\* document member of the same patent family

Date of the actual completion of the international search

18 March 1997

Date of mailing of the international search report

04.04.97

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. ( - 31-70) 340-2040, Tx. 31 651 epo nl.  
Fax: ( - 31-70) 340-3016

Authorized officer

Isert, B

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/18235

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>FASEB J, vol. 5, no. 4, 1991, page a476 XP000651989 KRAUSS ET AL.: "Prostanoid FP-receptor mediated contractions of the cat iris sphincter depend on Calcium influx" * see the abstract 609 *</p> <p>---</p>	1-16
A	<p>BR. J. PHARMACOL., vol. 104, 1991, pages 541-549, XP000651988 GILES H. ET AL. : "A comparative study of the prostanoid receptor profile of 9alpha11beta-prostaglandin F2 and prostaglandin D2 "" * see the abstract *</p> <p>-----</p>	1-16

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/18235

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0603800 A	29-06-94	AU 665287 B	21-12-95
		AU 5245093 A	30-06-94
		CA 2112027 A	22-06-94
		JP 6316525 A	15-11-94
		US 5565492 A	15-10-96
-----			
EP 0308135 A	22-03-89	AT 108330 T	15-07-94
		AU 600168 B	02-08-90
		CA 1324129 A	09-11-93
		CA 1328075 A	29-03-94
		DE 3850676 D	18-08-94
		DE 3850676 T	03-11-94
		DE 3868127 A	12-03-92
		DE 3876050 A	24-12-92
		EP 0289349 A	02-11-88
		EP 0455264 A	06-11-91
		ES 2052735 T	16-07-94
		GB 2209939 A,B	01-06-89
		JP 6080571 A	22-03-94
		JP 1151552 A	14-06-89
		JP 6067900 B	31-08-94
		JP 1858208 C	27-07-94
		JP 2000108 A	05-01-90
		US 5001153 A	19-03-91
		US 5591887 A	07-01-97
		US 5106869 A	21-04-92
		US 5151444 A	29-09-92
		US 5166178 A	24-11-92
		US 5212200 A	18-05-93
		US 5221763 A	22-06-93
		OA 9028 A	31-03-91
-----			

**This Page Blank (uspto)**